REMARKS

Support for amendments to the claims is found in the Specification as filed, as follows:

Claim	Phrase	Support in Specification as Filed
1	homogeneous system	Pate 2, line 25
	multi-chamber stack	Page 2, lines 9-10
	an inoculum of at least $0.7x10^6$ cells/ml in an initial volume of 1/10 to 1/6 of the multi-chamber stack final volume	Page 6, line 31 - page 7, line 1
	amplifying the cell number by adding a volume of complete medium corresponding to that contained in the multi-chamber stack	Page 7, lines 8-12
	recovering at least $1x10^9$ cells grown in homogeneous conditions	Page 2, lines 24-26
25		Original Claim 8
26		Original Claim 6
27		Original Claim 12
28		Original Claim 8

Claims 2-4, 9, 16, and 19-24 are canceled without prejudice for reasons unrelated to patentability. No new matter has been added herewith. The following addresses the substance of the Office Action.

Indefiniteness

Claims 1-16 and 19-23 were rejected under 35 U.S.C. § 112, Second Paragraph as being indefinite. The following issues were raised:

A. Claim 1 was found to be indefinite because of the recitation of a process for the "expansion" of TALL lymphocytes. In addition, claim 1 was drawn to a method but the only step recited was considered to be unclear. Claim 1 has been amended to recite a process for "amplifying" cells, indicating that the number of cells in increased by cell division. The amended claim recites three

steps and specifies that the process is for amplifying TALL-104 cells by inoculating with TALL-104 cells under the conditions described.

B. Claim 2 was found to be indefinite in the recitation of a fermentation unit "for anchorage dependent cells". Claim 2 is canceled rendering the rejection moot.

C. Claims 4 and 7 were indefinite because they contained the trademark Cell Factory™ and a trade name does not identify or describe the goods associated with the trade name. Claim 4 is canceled and claim 7 is amended by replacing the trade name with the general description "multi-chamber stack".

D. Claims 8-9 were found to be indefinite because it was unclear how a cell could be simultaneously a TALL-104 call and also be genetically modified. Claim 8 is amended to remove the Markush language that previously included various types of TALL cells. The claim is dependent on amended Claim 1, which is limited to TALL-104 cells. Amended Claim 8 recites that said TALL-104 lymphocytes <u>are</u> genetically modified. Thus, there is no ambiguity about the nature of the cells. Claim 9 is cancelled.

E. Claim 5 was found to be indefinite because of the limitation "the homogeneous system" since there was no antecedent basis in the claim or in claims 1 and 3. Claim 5 is amended to remove the phase.

F. Similarly, Claim 6 was found to be indefinite because of the phrase "the inoculum" since there was no antecedent basis in the claim or in claims 1 and 5. Amended Claim 1 now recites an inoculum of at least $0.7x10^6$ cells/ml, which provides antecedent basis for the term "the inoculum".

G. Claim 6 was found to be indefinite because a broad limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite. Thus, Claim 6 is amended to limit the density of inoculum to one limitation "at least $0.75x10^6$ cells/ml" and the harvest density is described by the singular limitation "lower than $2x10^6$ cells/ml".

H. Similarly, Claims 10 and 20 were also found to be indefinite because a broad limitation together with a narrow range or limitation that falls within the broad

range or limitation (in the same claim) is considered indefinite. Claim 10 is amended to recite the one limitation for human serum "comprises 10% maximum human serum". Claim 20 has been canceled.

I. Claims 10 and 20 recite the limitations "the complete culture medium" and "the cell factory" but there was insufficient antecedent basis for these limitations. Amended Claim 1 refers to "complete culture medium" providing antecedent basis for "the complete culture medium". Claim 10 is amended to recite "the multi-chamber stack" to be in accord with amended Claim 1 which recites "a multi-chamber stack."

J. Claim 12 recited the limitation "the homogeneous system" without antecedent basis. Amended Claim 1 now recites "a homogeneous system" providing proper antecedent basis.

K. Claims 14 and 22 recite the limitation "the bag filling collet" without antecedent basis. Claim 14 is amended to recite "a bag filling collet" to circumvent the need for antecedent basis. Claim 22 has been canceled.

L. Claim 23 recites the limitation "the process for the preparation of a therapeutic dose" without proper antecedent basis. Claim 23 is canceled rendering the rejection moot.

In light of the amendments to the claims and the remarks above, the Applicants respectfully request removal of the rejections under 35 U.S.C. § 112, Second Paragraph.

Obviousness

Visonneau et al. in view of Gambacorti-Passerini et al.

Claims 1-10, 12-13, 15-16, 19-21 and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Visonneau et al. 2000, in view of Gambacorti-Passerini et al. 1988. The Examiner states that Visonneau et al. teaches a method of preparing a therapeutic dose of the human killer cell line TALL-104, but that the reference does not teach growing at least $1x10^9$ cells in a Cell Factory™, nor using culture medium comprising human serum. The Examiner cites Gambacorti-Passerini et al. as teaching culturing cells in a 10 floor multi-tray Cell Factory™ with a range of concentrations of homologous human serum (2.5%, 5% and 10%). Referring to Table 6, the Examiner states that the Gambacorti-Passerini et al. teaches that the

procedure results in the recover of 63% of the starting cells at the end of culture (i.e., less than $2x10^6$ cells/ml at harvest time, and at least $1x10^9$ total cells. However, the procedure of the Gambacorti-Passerini et al. reference does not involve amplification of cell number. Rather, at least $1x10^9$ cells are seeded in the method disclosed by Gambacorti-Passerini et al. and, as the Examiner notes, about 63% of those input cells are recovered.

The method of the Gambacorti-Passerini reference is used for a different purpose than the problem solved by the present invention (i.e., it is related to activation of lymphocytes versus amplification of cell number in homogeneous conditions). The reference relates to conditions for LAK lymphocyte activation from peripheral blood cells with comparable cytotoxic efficiency as obtained in culture in flask, and discloses an initial cell seeding of $1.5 x10^6$/ml in the final Cell-Factory volume (3.5 L, for a 10 floor multitrays) (see p. 524, right col. "Large scale PBL activation"). However, Gambacorti-Passerini et al. does not disclose any volumetric expansion, as specified in the second step of amended Claim 1. Referring to page 7, lines 8-19 of the present Specification as filed, every 3-5 days, preferably every 4 days, during which time the cells generally duplicate, a volume of complete medium corresponding to that contained in the cell factory is added to continue the cell expansion and growth up to a max final volume of 2 litres/10-chamber cell factory and to a number of cells of 1.5 to $2.5x10^9$.

Specific details of the volumetric expansion carried out according to the present invention, which distinguish over the cited references, have been introduced into amended claim 1. For example, the initial inoculum conditions ("at least 0.7×10^6/ml") are optimal conditions, as described in the Specification and in the preferred embodiment of claim 4. This concentration is about half the Gambacorti-Passerini cell number at inoculum). Moreover, Claim 1 specifies how volumetric expansion is achieved (i.e., by the successive addition of volumes of fresh cell-culture medium). As discussed in the Specification at page 7, lines 20-26 , cell densities at inoculum and at harvest are critical for the large scale amplification and for the resulting cell cytotoxic activity of TALL lymphocytes.

The disclosure of the present application has addressed the problem of amplifying in homogeneous conditions a large number of cells and has solved this problem by volumetric addition of the culture medium within the multi-chambers tray. In this way, cell density is maintained at its optimum during all growth phases during cell doubling up to the harvest time.

Referring to the Specification as filed at page 11, lines 3-6, the process, at its completion, allows for a 10-fold amplification of cell number, with only a 8-fold volume increase, corresponding to a total number of 1.5 to 2.5 x 10^9 cells for a 10-chambers tray.

The Visonneau et al. and Gambacorti-Passerini references are silent regarding all the above mentioned conditions and, most importantly, do not even raise the problem of growing cells in homogeneous conditions, with a minimum number of handling operations that are essential for the therapeutic use of the TALL lymphocytes and that allow the process to become standardized with minimal variability among different batches of therapeutic doses.

The process as disclosed presents a number of additional advantages, for example, the minimal number of handling operations allows these cells to be grown in antibiotic free culture medium; the homogeneity of growth conditions for such a large number of cells allow a reduced number of quality controls (for both activity and sterility) and costs reduction, as mentioned in the Specification at page 11, lines 3-6.

In view of the amended claim 1 and the remarks above, the cited references neither anticipate nor make the claims obvious. The Applicants respectfully request removal of the rejection under 35 U.S.C. § 103(a).

Visonneau et al. in view of Gambacorti-Passerini et al. and Woolley et al.

Claim 11 is rejected under 35 U.S.C. § 103(a). The Examiner states that, although the combined teachings of Visonneau et al. and Gambacorti-Passerini et al. do not teach adding IL-2 to the cell culture every 48-96 hours, Wooley teaches that cytokine receptor expression by the cells in culture contributes to cytokine depletion of the medium, and that it would have been obvious to add IL-2. However, as noted above, the claims of the present application are directed to a different process than that disclosed by either of Visonneau et al. and Gambacorti-Passerini et al. individually or in combination. Thus, Claim 11, which is ultimately dependent on Claim 1, is not obvious in light of the cited references. Thus, removal of the rejection is respectfully solicited.

Visonneau et al. in view of Gambacorti-Passerini et al. and U.S. Patent 6,491,678

Claims 14 and 22 are rejected under 35 U.S.C. § 103(a) as being obvious because, while the combined teachings of Visonneau et al. and Gambacorti-Passerini et al. do not teach creating a sampling chamber in the frozen bags for the purpose of performing quality controls, the '678

patent teaches a freezing bag that can be sealed to create a sample chamber that can be detached without thawing and subsequent quality control. However, since claim 14 is ultimately dependent on Claim 1, it is not obvious in light of the cited references. Claim 22 has been canceled. Thus, removal of the rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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